Endokrynologia Polska
DOI: 10.5603/EP.2013.0030
Tom/Volume 64; Numer/Number 6/2013
ISSN 0423–104X

Gastroduodenal neuroendocrine neoplasms including *gastrinoma* — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

Nowotwory neuroendokrynne żołądka i dwunastnicy z uwzględnieniem *gastrinoma* — zasady postępowania (rekomendowane przez Polską Sieć Guzów Neuroendokrynnych)

Grażyna Rydzewska[1], Andrzej Cichocki[2], Jarosław B. Ćwikła[3], Wanda Foltyn[4], Alicja Hubalewska-Dydejczyk[5], Grzegorz Kamiński[6], Anna Lewczuk[7], Anna Nasierowska-Guttmejer[8], Ewa Nowakowska-Duława[9], Joanna Pilch-Kowalczyk[10], Anna Sowa-Staszczak[11], Beata Kos-Kudła[4]

and other participants of the Consensus Conference (affiliations at the end of the paper)
Elżbieta Andrysiak-Mamos, Tomasz Bednarczuk, Jolanta Blicharz-Dorniak, Marek Bolanowski, Jarosław Ćwikła, Andrzej Deptała, Daria Handkiewucz-Junak, Marek Hartleb, Michał Jarząb, Arkadiusz Jeziorski, Dariusz Kajdaniuk, Aldona Kowalska, Robert Król, Leszek Królicki, Jolanta Kunikowska, Katarzyna Kuśnierz, Paweł Lampe, Dariusz Lange, Magdalena Londzin-Olesik, Przemysław Majewski, Bogdan Marek, Gabriela Mełeń-Mucha, Andrzej Nowak, Waldemar Patkowski, Violetta Rosiek, Marek Ruchała, Sławomir Rudzki, Phillipe Ruszniewski, Teresa Starzyńska, Katarzyna Steinhof-Radwańska, Janusz Strzelczyk, Wojciech Zajęcki, Piotr Zdunowski, Anna Zemczak

[1]*Clinical Department of Internal Medicine and Gastroenterology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland*
[2]*Department of Oncological Surgery, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw Branch, Poland*
[3]*Department of Radiology Faculty of Medical Sciences, University of Varmia and Masuria, Olsztyn, Poland*
[4]*Division of Endocrinology, Department of Pathophysiology and Endocrinology. Medical University of Silesia, Katowice, Poland*
[5]*Chair and Department of Endocrinology, Jagiellonian University Collegium Medicum, Krakow, Poland*
[6]*Department of Endocrinology and Radioisotopic Therapy, Military Institute of Medicine, Warsaw, Poland*
[7]*Department of Endocrinology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland*
[8]*Department of Pathomorphology, Central Clinical Hospital of the Ministry of Interior, Warsaw, and Jan Kochanowski University, Kielce, Poland*
[9]*Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland*
[10]*Department of Radiology, Medical University of Silesia, Katowice, Poland*
[11]*Nuclear Medicine Unit, The University Hospital, Krakow, Poland*

Abstract
This paper presents the updated Polish Neuroendocrine Tumour Network expert panel recommendations on the management of neuroendocrine neoplasms (NENs) of the stomach and duodenum, including gastrinoma. The recommendations discuss the epidemiology, pathogenesis and clinical presentation of these tumours as well as their diagnosis, including biochemical, histopathological and localisation diagnosis. The principles of treatment are discussed, including endoscopic, surgical, pharmacological and radionuclide treatment. Finally, recommendations on patient monitoring are given. **(Endokrynol Pol 2013; 64 (6): 444–458)**

Key words: *neuroendocrine neoplasms; stomach; duodenum; gastrinoma; diagnostics; therapy; guidelines*

Streszczenie
W niniejszej pracy przedstawiono uaktualnione zalecenia grupy ekspertów Polskiej Sieci Guzów Neuroendokrynnych dotyczące zasad postępowania w nowotworach neuroendokrynnych żołądka i dwunastnicy z uwzględnieniem gastrinoma. Omówiono epidemiologię, patogenezę i obraz kliniczny tych nowotworów. Przedstawiono zalecenia dotyczące zasad postępowania diagnostycznego, z uwzględnieniem diagnostyki biochemicznej, histopatologicznej oraz lokalizacyjnej. Uwzględniono także zasady postępowania terapeutycznego, w tym leczenie endoskopowe i chirurgiczne, oraz omówiono możliwości leczenia farmakologicznego i radioizotopowego. Przedstawiono także zalecenia odnośnie monitorowania chorych z NEN żołądka, dwunastnicy z uwzględnieniem gastrinoma. **(Endokrynol Pol 2013; 64 (6): 444–458)**

Słowa kluczowe: *nowotwory neuroendokrynne; żołądek; dwunastnica; gastrinoma; diagnostyka; terapia; zalecenia*

Prof. Beata Kos-Kudła M.D., Ph.D., Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Ceglana St. 35, 40–952 Katowice, Poland, tel./fax: +48 32 358 13 66, e-mail: endoklin@sum.edu.pl

1. Epidemiology and pathogenesis

1.1. Neuroendocrine neoplasms of the stomach

Neuroendocrine neoplasms (NEN) constitute approximately 1% of all neoplasms of the stomach, and approximately 23% of all gastrointestinal tumours of this type [1]. The prevalence is estimated as 1–2 cases per 1,000,000 people per year, without any significant predominance of either sex (1.2/1,000,000 males, 1.8/1,000,000 females). In recent years there has been an 8–9-fold increase in the incidence of gastric NENs (g-NENs) as a result of increased detectability due to the availability of endoscopic techniques [2]. In the stomach, four clinical and pathogenetic types of g-NENs are found, with differences in the clinical and histopathological picture, as well as in diagnostic and therapeutic management.

Pathogenesis

Type 1 and 2 tumours arise from the enterochromatoffin-like (ECL) cells of the gastric mucosa in response to chronic, excessive secretion of gastrin. Secondary hypergastrinemia, caused by achlorhydria accompanying atrophic gastritis, is responsible for the development of g-NENs type 1. Primary hypergastrinemia in Zollinger-Ellison syndrome (ZES), occasional or associated with multiple endocrine neoplasia 1 (MEN1), is responsible for type 2 g-NENs. Gastrin and its derivatives stimulate proliferation, migration and differentiation of ECL cells, which leads to their hyperplasia and dysplasia [2]. In patients with MEN1, the transforming factor can be a menin defect. In the course of atrophic gastritis, no such factor has been determined. It is possible that protein inhibiting apoptosis BCL2, protein 53 (p53), fibroblast growth factor (FGF), transforming growth factor-α (TGF-α), and incorrect function of the REGL protein (inhibiting proliferation of ECL cells) could play a role [3].

Type 1

Gastric neuroendocrine neoplasms type 1 (70–80% of g-NENs) are associated with atrophic gastritis. They occur in less than 1% of patients, more often in women, and are diagnosed mostly between the ages of 40 and 60. In the future, the availability of endoscopic examination and conducting gastroscopy in patients with autoimmune diseases will lower the age of patients diagnosed with type 1 g-NEN [4,5].

They are diagnosed during an endoscopic examination performed due to dyspeptic symptoms or anaemia, more frequently due to macrocytic than iron-deficiency anaemia [5]. 65% of cases are multiple polyps of < 1 cm in diameter or microcarcinoids found in the gastric mucosa. In 70–85% they belong to the NEN G1 group, according to the World Health Organisation (WHO) 2010 classification [6, 7]. They are rarely invasive [2]. They are almost always slowly growing tumours with a good prognosis (up to 100% of patients with ten-year survival). They are non-functional, although less than 1% of patients with type 1 g-NENs present the symptoms of atypical carcinoid syndrome.

Type 2

This type constitutes 5–6% of gastric neuroendocrine tumours. It is a response to hypergastrinemia in the course of duodenal or pancreatic gastrinoma. In 23–29% of cases, it is part of MEN1 syndrome. In 1–3% of patients, it is a sporadic form of gastrinoma [2, 5, 8]. Zollinger-Ellison syndrome (ZES) is clinically present. Neoplasms are usually small (< 1–2 cm) and frequently multiple, located in the fundus and body of the stomach, only occasionally in the gastric cardia. They are classified as well-differentiated NENs (G1/G2 according to WHO 2010), with a good prognosis, regardless of the presence of metastases in as many as 35% of patients at the time of diagnosis [8].

Type 3

They are tumours occurring in 14–25% of cases, without any specific predisposing factors. They are more frequent in males over 50 years of age. They are single, of > 2 cm in diameter, with ulceration on the surface, located in the fundus and body of the stomach. They are classified as gastric neuroendocrine carcinomas (g-NEC according to WHO 2010). In 100% they are associated with metastases to the regional lymph nodes and liver. Deaths due to g-NEC occur in 25–87% of cases, depending on the level of differentiation and the presence of metastases [1].

Type 4

Presently, a division of gastric neuroendocrine neoplasms type 3 into subtypes 3 and 4 is suggested. Type 3 includes sporadic, non-functional tumours, whereas type 4 constitute poorly differentiated carcinomas, or carcinomas arising from cells producing ACTH, serotonin, as well as mixed, endo-exocrine carcinomas [2, 5]. From the clinical point of view, the clinical course of neoplasms type 3 and 4 is similar, and the division is of limited consequence for the choice of treatment.

1.2. Duodenal neuroendocrine neoplasms

According to American statistics, they constitute 2–3% of all gastrointestinal tumours [2, 9]. In 50–70% they are well-differentiated NENs (G1 according to WHO 2010). Five types of duodenal neuroendocrine neoplasms (d-NEN) can be distinguished [9]. They include: i) gastrinoma (27–58%); ii) non-functional neoplasms with positive results of immunohistochemical

tests for serotonin and calcitonin; iii) somatostatin (SST) secreting tumours (23–75%); iv) poorly differentiated duodenal carcinomas; and v) neoplasms of the gangliocytic paraganglioma type (rare). Some authors exclude from this group tumours located in the ampulla of Vater and its area (approximately 20% of NENs), whose clinical course rather resembles pancreatic neoplasms [9]. Over 90% of NENs are located in the duodenal bulb (58%) and descending duodenum (33%). Tumours belonging to d-NENs are usually small (1.2–1.5 cm), limited to the mucosa and submucosa, but at the moment of diagnosis in 40–60% of cases regional lymph nodes metastases are present. Hepatic metastases occur in less than 10% of patients. Multiple d-NENs suggest MEN1 [8].

2. Clinical characteristics

2.1. Gastric neuroendocrine neoplasms

Type 1 g-NENs are not characterised by a specific clinical picture. It is usually diagnosed during gastroscopy performed due to dyspeptic symptoms. The course of the disease is usually mild, and after endoscopic or surgical treatment it only requires a periodic endoscopic surveillance [6].

In type 2 g-NENs, the symptoms of ZES dominate (described for gastrinoma). Screening tests for MEN1 syndrome, described in the General Section, are necessary [8].

G-NECs are clinically manifested by abdominal pains, anaemia and weight loss. Their course is malignant and they are usually disseminated at the diagnosis [3].

Gastric neuroendocrine neoplasms very rarely (< 1%) present the symptoms of atypical carcinoid syndrome (concomitant hepatic metastases). Flushing usually lasts longer and is accompanied by lacrimation, often with lowered arterial pressure. Unlike the typical carcinoid syndrome, excess histamine can cause overgrowth of the facial skin ('leonine facies') and its bruising. Endocardial damage may also occur [10].

2.2. Duodenal neuroendocrine neoplasms

2.2.1. Gastrinoma

Gastrinomas are neuroendocrine neoplasms located in the duodenum (70%), pancreas (25%), and rarely (5%) in other sites (stomach, liver, ovary, lung), secreting gastrin and causing clinical ZES. Hypergastrinemia results in hypersecretion of gastric acid, and, consequently, in peptic ulcer disease and gastroesophageal reflux disease with a severe course [11, 12].

Gastrinomas are well-differentiated neoplasms (NEN G1/G2).

Depending on their location and possible concomitant MEN1, gastrinomas can be characterised as follows [8, 12–14].

Duodenal gastrinomas:
- 50–88% of gastrinomas in sporadic form are located in the duodenum;
- 70–100% of gastrinomas in MEN1 are located in the duodenum;
- are small (77% < 1 cm);
- demonstrate local invasiveness;
- are usually located in the duodenal bulb and descending duodenum;
- are associated with metastases to the nearest lymph nodes;
- hepatic metastases are rare (5–10%).

Pancreatic gastrinomas:
- are large (on average 3.8 cm, 6% < 1 cm);
- can be located in any part of the pancreas;
- are associated with frequent hepatic metastases (25–35%).

Gastrinoma in the course of MEN1/ZES:
- 20–30% of patients with ZES are diagnosed with MEN1;
- MEN1/ZES in 70–100% are situated in the duodenum, tumours are almost always multiple;
- 15% demonstrate aggressive clinical course;
- the average age at diagnosis is 32–35 years (for the sporadic form: 48–55 years);
- in 45% of patients, ZES symptoms precede by a few years symptomatic hypercalcemia;
- in 25% of MEN1/ZES patients, the family history of MEN1 is negative.

Zollinger-Ellison syndrome should be suspected in patients [12]:
- with multiple ulcers of the upper part of the gastrointestinal tract, with unusual location;
- with relapses after treatment;
- with concomitant severe oesophagitis;
- with negative H. pylori test results;
- with complications of the disease (gastrointestinal tract perforation, bleeding);
- with diarrhoea;
- with thickening of the gastric folds (present in 92% of ZES patients).

The most common symptoms include persistent pain in the upper abdomen (in 66% of patients), nausea (in 38%), vomiting (in 24%), diarrhoea (in 76%), which disappears after the use of protein pump inhibitors (PPI) — a very characteristic feature — weight loss (in 12%), and gastrointestinal bleeding. There are no differences between the clinical symptoms of pancreatic and duodenal gastrinoma [12].

Helicobacter pylori infection is less frequent in ZES patients (in 24–48% of patients) compared to idiopathic peptic ulcer disease (in 90% of patients). Therefore, negative results of *H. pylori* tests in patients with recurrent peptic ulcer disease who do not receive

NSAIDs or acetylsalicylic acid should be suggestive of gastrinoma [15].

ZES diagnosis requires the evidence of hypergastrinemia under fasted conditions, with hypersecretion of hydrochloric acid, or low gastric pH (pH < 2). In practice, the diagnostics starts with determination of serum gastrin level under fasted conditions (FSG), which is increased in 98% of ZES patients. The evidence of hypergastrinemia is not sufficient to diagnose ZES, as there are reasons for increased gastrin level other than gastrinoma [5, 8]:

— with hypo/achlorhydria — atrophic gastritis, using PPI;
— with hyperchlorhydria: *H. pylori* infection, pyloric stenosis, renal failure, antral G-cell syndromes, short bowel syndrome.

In 40–60% of patients with ZES, FSG value is lower than ten times the normal gastrin level under fasted conditions, and it is comparable to gastrin levels in the course of *H. pylori* infection.

Therefore, the effective eradication of *H. pylori* is necessary before gastrinoma diagnosis can be established [8].

Proton pump inhibitors (PPI) and histamine H2-receptor antagonists increase gastrin and CgA levels in the blood, so PPI should be discontinued 10–14 days before the planned test. In patients with suspected gastrinoma, PPI can be substituted in this period with oral H2-receptor antagonists, but it is recommended that they are also discontinued at least 48 hours before the examination [8].

Gastrinoma can be diagnosed if the gastrin levels under fasted conditions are over ten times the upper limit of normal, and gastric pH is < 2. In most cases, increased gastrin level is accompanied by increased serum CgA concentration. The blood for gastrin determination should be drawn under fasted conditions. If gastrin concentration under fasted conditions is increased less than ten times, and pH of the gastric juice is ≤ 2, the secretin stimulation test should be performed. Secretin is administered under fasted conditions, intravenously, at a dose of 2.0 units/kg bw. Gastrin is determined at proper intervals, expressed in minutes relative to the moment of secretin administration: –15 min, –1 min, +2 min, +5 min, +10 min, +15 min, +20 min, and +30 min. Gastrinoma diagnosis is confirmed by an increase in gastrin level by more than 120 pg/mL, at any point of the test, in relation to the baseline value. For this value of increase in gastrin concentration, the sensitivity of the secretin stimulation test is 94%, and the specificity is 100%. Increasing the value of the diagnostic gastrin increment to 200 pg/mL reduces the test sensitivity to 82% [8].

The gastrin stimulation test with intravenous calcium gluconate is less sensitive, less specific and associated with more adverse reactions. It is rarely performed, only if conducting the secretin stimulation test is impossible or if its result is negative, while the clinical suspicion of gastrinoma is strong [16].

Determination of gastrin level on consecutive days demonstrates the referential values in less than 0.5% of patients with ZES. Gastric juice pH above 3, on the other hand, is a strong indicator excluding the presence of gastrinoma. As in 20–25% of cases gastrinoma is an element in MEN1 syndrome, every patient with ZES should undergo screening tests for MEN1 described in *General Recommendations*.

The clinical course is aggressive in approximately 25% of sporadic and 15% of ZES/MEN1 gastrinoma patients. The following constitute poor prognostic factors [16]:

— inadequate control of gastric acid hypersecretion,
— liver metastases,
— female sex,
— sporadic form,
— short time interval between initial symptoms and diagnosis,
— very high FSG,
— large size (1–3 cm) of the primary tumour,
— pancreatic location of the primary tumour,
— ectopic ACTH secretion in the course of gastrinoma,
— bone metastases,
— angioinvasion and perineurium infiltration in histologic examination.

2.2.2. Other duodenal neuroendocrine neoplasms

Clinical symptoms of other duodenal NENs are varied: abdominal pain (in 9–64% of patients), bleeding from the upper gastrointestinal tract (in 11–28%), jaundice (in 7–32%), anaemia (in 11–28%), vomiting (4–8%) and duodenal stenosis (in 1% of patients). Jaundice, bile duct dilatation enlargement, vomiting and diarrhoea often accompany NENs located in the proximity of the ampulla of Vater [16]. If duodenal neuroendocrine neoplasms present symptoms of carcinoid syndrome (in case of hepatic metastasis), the syndrome is usually atypical [10] (described earlier, with gastric carcinoids).

Neuroendocrine neoplasms secreting ectopic hormones

In the literature there are reports describing duodenal neuroendocrine neoplasms with Cushing's syndrome (5–15% of patients), predominantly already in IV stage of clinical advancement and with unfavourable prognosis, with acromegaly (ectopic GRH secretion), insulinoma and glucagonoma symptoms [17].

2.2.3. Non-functional duodenal neuroendocrine neoplasms

They do not produce any hormone-dependent clinical symptoms. However, immunohistochemical examination demonstrates the presence of gastrin, serotonin, calcitonin and somatostatin in the tumour. These neoplasms constitute 70-98% of duodenal tumours. They include gangliocytic paragangliomas, which are most frequently located in the duodenal bulb area. They are usually large and benign tumours invading the muscular layer [18].

3. Diagnostics

3.1. Biochemical diagnostics

3.1.1. Gastric neuroendocrine neoplasms

Biochemical diagnostics of type 1 g-NENs:

— increased serum chromogranin A (Cg) [19] (**evidence level 5*);
— high gastrin level under basic conditions [10] (**evidence level 5*);
— increased daily urinary excretion (5-HIAA, 5-hydroxyindoleacetic acid) (**evidence level 5*);
— serum serotonin concentration. Determination should be performed only in patients with atypical (rarely with typical) carcinoid syndrome (**evidence level 5*);
— assessment of vitamin B12 level in patients with hypergastrinemia (**evidence level 3*).

Determination of b-hCG, human chorionic gonadotropin (presence in the granules of tumour cells, possible ectopic secretion) may be useful for the diagnosis [18].

In biochemical diagnostics of type 2 NENs:

To confirm ZES, the following tests should be performed:

— serum gastrin level under basic conditions (**evidence level 3*);
— assessment of serum gastrin level after stimulation, i.e. the test with secretin (2 units/kg bw i.v.) or calcium gluconate in uncertain cases, (**evidence level 3*);
— assessment of serum gastrin level in patients after surgery due to gastrinoma, 3–12 months after the surgery, then follow-up tests every 6–12 months for 3–4 years (**evidence level 5*).

Other:

— determination of serum CgA concentration (**evidence level 5*);
— in uncertain cases concerning differentiation of the causes of secondary hypergastrinemia — determination of gastric pH (pH< 2) [20] (**evidence level 4*);
— in the case of suspected MEN1 syndrome, screening tests described in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*) should be performed. Concomitant MEN1 syndrome requires confirmation in genetic tests [8] (**evidence level 4*).

Biochemical diagnostics of type 3 NENs (NEC):

— determination of serum CgA level is recommended (**evidence level 5*);
— daily urinary excretion of 5-HIAA in the case of atypical carcinoid syndrome (**evidence level 5*).

3.1.2. Duodenal neuroendocrine neoplasms

— determination of CgA (**evidence level 5*);
— gastrin in patients with ZES, in justified cases the test with secretin [19] (**evidence level 3*);
— if clinical symptoms suggestive of ectopic hormone production by duodenal NEN occur, the following hormones should be determined (regardless of clinical symptoms characteristics): adrenocorticotropic hormone (ACTH) and cortisol, insulin and peptide C, as well as glucagon, insulin-like growth factor 1 (IGF 1) and growth hormone (GH), also in functional tests [19] (**evidence level 5*);
— in patients with duodenal NEN and clinical characteristics of MEN1 syndrome, positive family history of MEN1, and multi-focal duodenal NEN, genetic tests for the presence of germinal menin gene mutation should be performed. Examination of somatic mutation in the tumour is not recommended [14] (**evidence level 4*).

Minimal consensus statement on biochemical tests:

*CgA — regardless of clinical symptoms (*evidence level 5);*
*Gastrin — in ZES (*evidence level 3);*
*5-HIAA — in typical and atypical carcinoid syndrome (*evidence level 3).*

3.2. Pathomorphological diagnostics

3.2.1. Pathogenesis

Gastric NENs are usually non-functional tumours arising from enterochromaffin-like (ECL) cells producing histamine, and are most frequently found in the fundus and body of the stomach. Less common are gastrin-producing G cells, present in large quantities in the pylorus, somatostatin-producing D cells, diffused in small quantities throughout the stomach, and serotonin-producing EC cells, very rarely found in the stomach. Gastric NENs are divided into four types, according to their clinical and morphological characteristics [5, 21, 22]. Table I presents the characteristics of each group of neoplasms.

** evidence level according to CEBM [59]*

Table I. *Types of gastric neuroendocrine neoplasms*
Tabela I. *Typy nowotworów neuroendokrynnych żołądka*

	Type 1	Type 2	Type 3	Type 4
Frequency	70–80%	rare	10–15%	Rare
Size	0.5–1.0 cm	Usually up to 1.5 cm	Varied, most of them > 2 cm	Large tumour mass
Number of tumours	Multiple, small nodules, polyps	Multiple	Single	Single
Location	Body	Body	Throughout the stomach	Throughout the stomach
Associated conditions	Hypergastrinemia, chronic atrophic gastritis, ECL hyperplasia	MEN1 , hypergastrinemia, Zollinger-Ellison syndrome	Sporadic	Sporadic
Clinical course	Usually benign, limited to mucosa, submucosa	30% metastases	71% of tumours > 2cm Invasion of muscularis propria, vessels and lymph nodes	Highly malignant carcinoma, usually with metastases, unfavourable prognosis
Demographic characteristics	70–80% females 50–60 years of age	females = males mean age 50 years	More frequently males Mean age 55 years	More frequently males

Type 1 gastric NENs occur most frequently. It develops in the gastric mucosa in the course of atrophic gastritis with concomitant hypergastrinemia in the form of multiple polyps and nodules in the body of the stomach. The precursor is a linear or nodular hyperplasia of ECL cells, associated with an increased risk of ECLoma. Type 1 tumours are usually benign and can disappear after resection of the prepyloric part, although currently this approach is not recommended [23].

Lymph nodes metastases are sporadic and usually develop in the course of tumours larger than 2 cm in diameter. In the case of multiple gastric polyps, pathomorphological diagnosis requires differentiation of ECLoma from other lesions such as hyperplastic or inflammatory polyps, adenomas or early carcinoma type 0-I. Biopsy of different lesions is recommended, particularly of those which differ in macroscopic appearance, and from the fundus and body of the stomach, in order to verify atrophic inflammation.

Type 2 NENs are rare, and usually occur in the course of MEN1 with Zollinger-Ellison syndrome. Unlike type 1, in 30% of cases lymph nodes metastases are present. The tumours are usually of more than 2 cm in diameter, invading muscularis propria and demonstrating angioinvasive properties.

Germinal mutation tests are recommended in patients with suspected MEN1 in cases with ECLoma and Zollinger-Ellison syndrome, or with a family history suggestive of MEN1 or multiple tumours without the evidence of atrophic gastritis. Examination of somatic mutations in gastric NENs is not recommended.

Gastric NENs type 1 and 2 are usually well-differentiated neuroendocrine neoplasms (NEN G1, NEN G2).

Type 3, neuroendocrine carcinoma (NEC) is the second most common gastric neuroendocrine neoplasm. It is a sporadic tumour, not associated with atrophic inflammation or hyperplasia of neuroendocrine cells. Neoplasms of more than 2 cm in diameter, angioinvasion and infiltration of the muscularis propria are the risk factors for metastasis.

Type 4, neuroendocrine carcinoma (NEC) is a sporadic, highly malignant neuroendocrine cancer, manifesting in the form of a large tumour mass, usually with metastases at the time of diagnosis. This neoplasm is characterised by unfavourable prognosis, fast progression and aggressive course.

3.2.2. Diagnostic algorithm

Diagnosis of gastric NENs is based on the histopathological examination of polyps after their endoscopic resection in the case of NENs type 1 and 2 (NEN G1, NEN G2), or the surgical material obtained after resection of the stomach and lymph nodes in gastric NENs type 3 and 4 (NECs) [7, 24–26].

A. Microscopic assessment of type 1 gastric NENs:
A type 1 gastric NEN is a well-differentiated neuroendocrine neoplasm with the macroscopic appearance of a polyp or polyps. In such cases, NEN G1 are usually diagnosed, and only sporadically NEN G2.

In microscopic assessment, the following parameters need to be determined:

— type of the neoplasm according to the WHO classification;
— differentiation grade G on the basis of the Ki-67/MIB1 proliferation index and the number of mitotic figures;

— polyp resection margin;
— angioinvasion properties.

B. Macroscopic assessment of surgical material includes the following parameters:

1. Size of the stomach fragment obtained for examination, with the description of the tumour's location relative to resection margins.

2. Tumour size (if possible, in three dimensions). Condition of the mucosa at the tumour site (ulcerated/non-ulcerated). Tumour position relative to the stomach wall layers; tumour cross-sectional image, taking into consideration the areas of necrosis and extravasations.

3. Number and size of lymph nodes.

4. Image of the mucosa in the remaining part of the slide (all changes need to be examined histopathologically).

5. Presence of other lesions in the stomach wall.

6. Width of surgical margins.

C. Microscopic assessment of the surgical material is based on the assessment of the following parameters:

1. Histological type of the NEN according to the WHO 2010 classification.

2. The histological grade G according to ENETS/WHO 2010.

3. Pathomorphological staging pTNM according to ENETS and AJCC/UICC (Table II).

4. Assessment of surgical margins.

5. Lesions in the gastric mucosa apart from the tumour:
— presence/absence of atrophic inflammation,
— hyperplasia of ECL cells,
— other changes.

6. Assessment of immunohistochemical expression of neuroendocrine markers chromogranin A and synaptophysin, as well the Ki67/MIB proliferative activity (obligatory)

7. Immunohistochemical assessment of the markers: NSE, CD56, CDX2, serotonin (conditional).

Histopathological types of NENs according to the WHO 2010 classification and the histological grade (G) according to the ENETS/WHO 2010 criteria are presented in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*).

Table II presents pTNM classification according to AJCC/UICC 2011.

Table II. ***Classification pTNM according to UICC/AJCC, 2011***
Tabela II. ***Klasyfikacja pTNM według UICC/AJCC, 2011***

pT feature	Comment
TX	Primary tumour cannot be evaluated
T0	No evidence of primary tumour
Tis	In situ tumour/neoplasm (< 0.5 cm), limited to mucosa
T1	Tumour invades mucosa and/or submucosa, tumour ≤ 1 cm
T2	Tumour invades muscularis propria or tumour > 1 cm
T3	Tumour invades subserosa
T4	Tumour invades serosa or other organs or adjacent structures

3.2.3. Duodenal neuroednocrine neoplasms

Pathogenesis

Duodenal endocrine neoplasms are rare, constituting approximately 1–3% of primary neoplasms of this organ and 5.7–7.9% of gastrointestinal neuroendocrine neoplasms. Over 90% of NENs are located in the proximal duodenum, and approximately 20% in the vicinity of the ampulla of Vater [27, 28]. These neoplasms are usually small (up to 2 cm in diameter), single lesions limited to the mucosa and submucosa. Intramural, extensively infiltrating tumours up to 5 cm [29, 30] have also been described. Multiple lesions, found in ca. 10% of cases, suggest the presence of MEN1 syndrome. In 40-60% of cases, regional lymph nodes metastases are found, and hepatic metastases in less than 10% [24, 28, 31, 32].

Duodenal neuroendocrine neoplasms are more frequently tumours producing active substances than non-active ones. They include functional tumours such as gastrinoma (48% of cases) and somatostatinoma (43%), as well as hormonally non-functional ones producing serotonin (27%) and calcitonin (9%). Approximately 50% of sporadic gastrin-producing NENs (*G cell NENs*) are hormonally functional tumours, causing clinical gastrinoma syndrome and associated with Zollinger-Ellison syndrome. In patients with sporadic gastrinoma, approximately 60–75% of neoplasms are located in the duodenum, and others in the pancreas. In MEN1 syndrome associated with Zollinger-Ellison syndrome, most gastrinoma tumours are located in the duodenum. The second type of duodenal neuroendocrine neoplasm, somatostatinoma, tends to arise near the ampulla of Vater, and in the microscopic picture is characterised by psammomatous bodies, usually not present in other duodenal NENs. According to the WHO classification, duodenal neuroendocrine neoplasms are usually well-differentiated NENs G1 (50% to 75% of cases), less often NEN G2 (25 to 50%), and only sporadically they are poorly differentiated neuroendocrine carcinomas (up to 3% of cases).

Grading of neuroendocrine neoplasms is conducted on the basis of mitotic activity (per ten high-power

fields) and proliferation activity measured using the Ki-67 index.

Diagnostic algorithm

A histopathological report from the assessment of the surgical material — duodenal neuroendocrine neoplasms:

A. Macroscopic description:

1. Size of the duodenum fragment obtained for examination, with the description of the tumour location relative to resection margins and surrounding tissues.

2. Tumour size (if possible, in three dimensions). Condition of the mucosa at the tumour site (ulcerated/ /non-ulcerated). Tumour position relative to the duodenal wall layers and adjacent tissues; tumour cross-sectional image, taking into consideration the areas of necrosis and blood extravasations.

3. Number and size of lymph nodes.

4. Image of the mucosa in the remaining part of the slide (all changes need to be examined histopathologically).

5. Presence of other lesions in the duodenal wall.

B. Microscopic description:

1. Histopathological diagnosis (considering all the properties mentioned in the classification):

— histological type according to the WHO 2010 classification;
— histological grading (G) according to ENETS/WHO 2010 (see General Recommendations for the Management of GEP NENs);
— pTNM pathomorphological staging;
— presence/absence of angioinvasion characteristics.

2. Tumour position relative to anatomical layers of the duodenal wall and adjacent tissue (depth of the invasion).

3. Width of surgical margins.

4. Lesions in the duodenal mucosa apart from the tumour.

5. Obligatory immunohistochemical examinations: chromogranin, synaptophysin and Ki-67/MIB1.

6. Conditionally — assessment of the neoplasm's neuroendocrine properties in the immunohistochemical examination (intensity and steadiness of reaction should be reported, and possibly, the manufacturer of the used reagents should be mentioned; in patients with MEN1 syndrome and gastrinoma located in the duodenum, immunohistochemical assessment of gastrin and other hormones expression, both in the primary tumour and in the metastatic foci, should be performed):

— gastrin, serotonin, SST (additionally PP, calcitonin, insulin, glucagon);
— S-100, NSE (in case of gangliocytic paraganglioma).

Fine-needle aspiration biopsy may be useful in the assessment of the stage of clinical advancement of the disease (diagnosis of neoplastic metastases in the lymph nodes and liver). Cytologic smears can also be used for immunocytochemical examinations.

TNM classification of duodenal neuroendocrine tumours [7]:

T — primary tumour

TX — primary tumour cannot be evaluated

T0 — no evidence of primary tumour

T1 — tumour invades lamina propria or submucosa and ≤ 1 in diameter (neoplasm limited to the ampulla of Vater for gangliocytic paraganglioma)

T2 — tumour invades muscularis propria or > 1 cm in diameter

T3 — tumour invades pancreas or retroperitoneum

T4 — tumour invades visceral peritoneum or other organs (for any T, add 'm' with multiple tumours)

N — regional lymph nodes

NX — regional lymph nodes cannot be assessed

N0 — no regional lymph nodes metastases

N1 — presence of lymph nodes metastases

M — distant metastases

M — distant metastases cannot be assessed

M0 — no distant metastases

M1 — distant metastases

Clinical advancement staging is presented in Table III.

Minimal consensus statement on pathomorphological examination:

Minimal histopathological report for gastroduodenal NEN should include:

— *histological type of the neoplasm according to the WHO classification, considering the division into well-differentiated neuroendocrine neoplasms (NEN G1 and NEN G2) and neuroendocrine carcinomas (NEC) or mixed neoplasms (MANEC);*
— *histological G grading referring to well-differentiated neoplasms (NEN G1, NEN G2)*
— *assessment of polyp resection or surgical margins in the surgical material;*
— *pTNM histopathological staging according to ENET and AJCC/UICC classifications (it is important to provide affiliation of the classification in each case).*

Histopathological diagnosis of NEN must be necessarily confirmed by immunohistochemical tests assessing expres-

** evidence level according to CEBM [59]*

Table III. *Disease staging for duodenal neuroendocrine tumours*
Tabela III. *Stopień zaawansowania klinicznego nowotworów neuroendokrynnych dwunastnicy (staging)*

Stage	Feature T	Feature N	Feature M
I	T1	N0	M0
IIa	T2	N0	M0
IIb	T3	N0	M0
IIIa	T4	N0	M0
III	any T	N1	M0
IV	any T	anyN	M1

*sion of the neuroendocrine markers: synaptophysin and chromogranin A, as well as the Ki-67 proliferative activity using the MIB1 antigen (*evidence level 3).*

3.3. Location diagnostics of gastroduodenal neuroendocrine neoplasms

3.3.1. Gastric neuroendocrine neoplasms

Gastric neuroendocrine tumours type 1:

— basic examination in imaging diagnostics is endoscopy of the upper gastrointestinal tract with biopsy and/or complete removal of the largest tumour for histopathological examination; also two samples from the antrum need to be obtained for histopathological examination, as well as four samples from the fundus/body of the stomach [2, 33, 34].
— It is also recommended to obtain a biopsy from the antrum and from the body of the stomach for a quick urease test if *Helicobacter pylori* infection was not assessed with the use of other methods;
— in the case of tumours > 1–2 cm and/or multiple tumours, endoscopic ultrasonography (EUS) should be performed before deciding on endoscopic treatment, in order to assess the depth of intramural invasion [6, 35].

To assess the disease staging, three-phase CT examination with water-filling of the stomach and after i.v. contrast administration needs to be performed as an initial (baseline) examination, and usually every six months, or depending on the clinical symptoms, as a surveillance examination during the clinical follow-up [36].

Gastric neuroendocrine tumours type 2:

— similarly to type 1 tumours, endoscopy of the upper gastrointestinal tract with biopsy and/or complete removal of a small tumour for histopathological examination should be performed, also two samples from the antrum need to be obtained for histopathological examination, as well as four samples from the fundus/body of the stomach in the case of larger and/or multiple tumours, and tests should be performed to determine the *Helicobacter pylori* infection;
— in the case of tumours > 1–2 cm and/or multiple tumours, endoscopic ultrasonography (EUS) should be performed in order to assess the depth of intramural invasion;
— to exclude the presence of metastases, the following tests should be conducted:
  • three-phase computed tomography (CT) examination with water-filling of the stomach and after i.v. contrast administration in order to determine the disease staging as an initial (baseline) examination, and usually every six months, or depending on the clinical symptoms, as a surveillance examination during clinical follow-up;
  • SRS test in order to determine the disease staging during the follow-up, usually every 9–12 months or depending on the clinical symptoms, and if discrepancies between clinical, biochemical and structural examination results occur. This test is necessary before introducing therapy with somatostatin analogues (SSA) analogues ('cold' and 'hot').

In the case of gastric neuroendocrine neoplasms type 3 (sporadic) and type 4:

— endoscopy of the upper gastrointestinal tract should be performed, and tumour samples obtained for diagnosis;
— endoscopic ultrasonography (EUS) may be used to assess the depth of intramural invasion, the presence of lymph nodes metastasis, and to confirm the diagnosis in histopathological examination of fine-needle aspiration biopsy (FNAB) material;

** evidence level according to CEBM [59]*

— ultrasonography (USG) of the abdominal cavity should be performed as an initial/surveillance examination (it enables identification of hepatic and lymph nodes metastasis with optimal conditions of examination of the abdominal cavity, mostly superficial lymph nodes or other superficial tissues invaded by the neoplastic process; it allows to obtain material for pathological examination, FNAB);
— three-phase CT examination with water-filling of the stomach and after i.v. contrast administration should be performed each time in order to determine the disease staging, as an initial (baseline) examination, and as a surveillance examination during the clinical follow-up, usually every 3–6 months, or depending on the clinical symptoms;
— magnetic resonance (MR) of the abdominal cavity before and after i.v. contrast administration should be performed if CT examination cannot be conducted (allergy to iodine agents is not an absolute contraindication for the test, which may be performed after proper antiallergenic premedication) [33, 37, 38]
— magnetic resonance of the spine or bone scintigraphy should be performed if any osseous metastases, visible on the CT scan, are suspected. If numerous bone metastases are present, 99TcMDP scintigraphic examination should be performed to assess the possibility of palliative radioisotope therapy (**evidence level 3*).

3.3.2. Duodenal neuroendocrine tumours:
— a sensitive method for detecting duodenal neuroendocrine tumours is endoscopy of the upper gastrointestinal tract, conducted with the use of straight/ /curved probes with biopsy and/or complete removal of the tumour for histopathological examination. In the case of hormonally functional tumours with characteristics of gastrinoma, upper gastrointestinal endoscopy may demonstrate specific lesions associated with gastric hypersecretion, such as multiple gastric and duodenal ulcers, and even small intestinal ulcers or severe reflux oesophagitis (Zollinger-Ellison syndrome) [33, 39].
— endoscopic ultrasonography (EUS) with optional fine-needle aspiration biopsy should be performed in the case of larger tumours, in order to assess the extent of intramural invasion, and in any non-diagnostic endoscopy [40–43].

To assess the disease staging, the following examinations need to be performed:
— three-phase computed tomography after oral administration of water in two stages — 500 mL half an hour before the test, and 500 mL immediately before the test, for optimal expansion of the gastroduodenal lumen, and after i.v. contrast administration [36]. The test should be performed in order to determine the disease staging, as an initial (baseline) examination, and as a surveillance examination during clinical follow-up, usually every six months, or depending on the clinical symptoms;
— SRS test should be performed in order to determine the disease staging during follow-up, usually every 9–12 months, or depending on the clinical symptoms, and if discrepancies between clinical, biochemical and structural examination results occur. This test is necessary before introducing therapy with SSA ('cold' and 'hot').
— if duodenal neuroendocrine tumours are not visible in structural and functional examinations, and in the case of hormonally functional tumours, intraoperative SRS and/or intraoperative USG are examinations of choice;
— magnetic resonance of the spine or bone scintigraphy should be performed if any osseous metastases, visible in CT or SRS, are suspected [44] (**evidence level 3*).

Minimal consensus statement on imaging:

Upper gastrointestinal endoscopy with histopathological examination of the obtained material and endoscopic ultrasonography are methods of choice in the diagnostics of most gastroduodenal neuroendocrine tumours.

Computed tomography of the abdominal cavity with contrast, magnetic resonance and receptor scintigraphy should be used to assess the disease staging and detect potential distant metastases.

*In patients with advanced disease (e.g. with hepatic metastases), bone scintigraphy, SRS and magnetic resonance of the spine should be performed (*evidence level 3).*

4. Treatment

4.1. Endoscopic and surgical treatment of gastroduodenal neuroendocrine tumours

4.1.1. Gastric neuroendocrine tumours

1. Well-differentiated neoplasms of less than 1 cm: only observation, necessary endoscopy every 12 months.

2. Well-differentiated neoplasms larger than 1 cm, in EUS test not invading muscularis propria: endoscopic mucosal resection (EMR) or endoscopic mucosal dissection (ESD), or surgical resection, depending on

** evidence level according to CEBM [59]*

the clinical situation. After endoscopic treatment, it is recommended to conduct surveillance examination every 12 months.

3. Neoplasms invading deep into the organ wall: surgical procedure of choice [6, 45].

4.1.2. Duodenal neuroendocrine tumours

If the disease is not metastatic, attempts should be made to remove all tumours within the duodenum.

In tumours smaller than 1 cm, not invading the muscularis propria in the EUS examination, after exclusion of metastasis: if it is possible from the technical point of view, and we have access to a centre with proper experience, they may be removed endoscopically. If not – surgical removal is possible.

Tumours larger than 2 cm and any tumour with lymph nodes metastasis, regardless of its size, should be managed radically by surgical treatment.

Tumours of 1–2 cm:

— without lymph nodes invasion: local excision,
— with invasion of lymph nodes: radical surgical procedure.

Neoplasms with hepatic metastases: if surgical excision or local ablation of metastases is possible, radical surgical procedure within the duodenum should be performed [46, 47].

4.1.3. Gastrinoma

Sporadic gastrinoma:

— if the disease is not disseminated, distal pancreatectomy should be performed if the tumour is located in the peripheral part of the pancreas;
— with the tumour located in the pancreatic head — if it is possible from the technical point of view, an attempt should be made to enucleate the tumour; if it is not possible, pancreatoduodenectomy should be performed;
— with the tumour located in the duodenal wall it is necessary to perform duodenectomy with tumour excision or pancreatoduodenectomy.

Gastrinoma in MEN1 (most frequently multiple) — radical treatment is rarely possible. If the disease seems to be limited, an attempt to perform a radical resection can be made.

Minimal consensus statement on surgical treatment.

*Surgery remains the only method with the potential to cure patients with neuroendocrine tumours of the stomach and duodenum. Tumours smaller than 1 cm and without signs of invasion can be observed in specialised centres. Tumours with a diameter of 1–2 cm can be excised locally by endoscopy or open or laparoscopic surgery. Tumours with signs of invasion and metastatic lymph nodes, as well as all tumours larger than 2 cm, should be treated like cancer i.e. by extensive radical surgery. In gastrinoma, we should try to remove all tumours located in the pancreas or duodenum, usually by pancreatoduodenectomy (*evidence level 4).*

4.2. Pharmacological treatment

4.2.2. Gastric neuroendocrine neoplasms

Gastric neuroendocrine neoplasms type 1

Patients with gastric NENs type 1 usually do not require pharmacological treatment [18]. Sometimes individual attempts are made to introduce treatment with somatostatin analogues, as they inhibit hypergastrinemia and prevent hyperplasia of ECL cells [20] (**evidence level 4*).

Gastric neuroendocrine neoplasms type 2
Zollinger-Ellison syndrome (ZES)

The aims of ZES therapy are: 1) to normalise secretion of hydrochloric acid, 2) to manage gastrinoma, 3) to treat gastric type 2 NEN (it develops in 13–30% of patients with ZES/MEN1) [8].

Excessive secretion of gastric acid in gastrinoma must be inhibited pharmacologically in all patients with gastrinoma, in order to prevent complications.

The treatment of choice involves proton pump inhibitors (PPI) (**evidence level 3*). All marketed PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) reveal similar effectiveness. Administration of PPI once or twice a day is effective in most patients. The recommended initial dose for omeprazole in sporadic forms of ZES is 60 mg once a day. In patients with ZES complications (MEN1 with hypercalcaemia, severe GERD symptoms, preceding Billroth II resection), higher doses of antisecretive medications are used (e.g. omeprazole 40–60 mg twice a day). During a long-term therapy with PPI, the serum levels of vitamin B12 should be monitored once a year, and more frequent bone fractures in this population should be taken into account [15].

Histamine H2-receptor antagonists may also be used in patients with ZES. Patients with gastrinoma require higher and more frequent doses than patients with idiopathic peptic ulcer disease. If oral administration of medications is not possible, PPI are administered intravenously. During intravenous treatment, high doses of histamine H2-receptor antagonists are also administered by constant intravenous infusion.

Long-acting somatostatin analogues are not first-line medications, and they should be used only in the case of PPI treatment-resistant, malignant gastrinoma (**evidence level 3*).

** evidence level according to CEBM [59]*

In MEN1 syndrome, surgical resection of the parathyroids in primary hyperparathyroidism reduces excessive secretion of hydrochloric acid [16].

Gastric neuroendocrine neoplasms type 3 and 4

There is no specific pharmacological treatment. Therapy with SST analogues and biotherapy are not recommended in the case of these tumours (**evidence level 5*). Rules for chemotherapy in NEC are described in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443).*

In the case of progression of neuroendocrine neoplasms G1 and G2, the following are used [15, 48]:

— therapy with short- or long-acting somatostatin analogues (**evidence level 3*);
— Everolimus 10 mg/day or sunitinib 37.5 mg/day in the case of gastrinoma (**evidence level 3*); the other neoplasms: everolimus 10 mg/day (**evidence level 4*);
— cytotoxic chemotherapy if no other therapeutic options are available — capecitabine, dacarbazine, 5-fluorouracil, interferon, temozolomide, or based on combinations containing streptozocin, 5-fluorouracil and doxorubicin (**evidence level 4*);
— PRRT — see below.

Loperamide, cholestil, pancreatic enzymes, cholestyramine, biphosphonates and corticosteroids may be used for symptomatic treatment, according to clinical indications [15].

Chemotherapy in the treatment of poorly differentiated gastric neuroendocrine neoplasms is similar to that used for therapy of small-cell carcinoma, i.e. the regimen based on the platinum derivatives (cisplatin or carboplatinum) and etoposide; in the case of progression, second-line chemotherapy should be considered (**evidence level 4*).

4.2.3. Duodenal neuroendocrine neoplasms

Treatment of gastrinoma should be analogous to that of type 2 gastric NENs, whereas other tumours — in particular disseminated ones, associated with carcinoid syndrome — should be treated like gastric tumours at the same stage of advancement.

Chemotherapy in the treatment of poorly differentiated duodenal neuroendocrine neoplasms is similar to that used for therapy of small-cell carcinoma.

Minimal consensus statement on pharmacotherapy:

1. Stomach

*Type 1 — eradication of H. pylori (*evidence level 3).*

*Type 2 — eradication of H. pylori, PPI, (*evidence level 3).*

*In the case of malignant gastrinoma, treatment with somatostatin analogues to be considered (*evidence level 5).*

*Type 3 — symptomatic treatment, chemotherapy (*evidence level 3).*

2. Duodenum

*ZES — PPI, H2 blockers (*evidence level 3).*

*ZES/MEN1 — PPI, treatment of hypercalcaemia (*evidence level 3).*

*Hormonally non-functional neoplasms — symptomatic treatment (*evidence level 4).*

*Functional neoplasms — treatment specific for the type of hormonal activity, somatostatin analogues (*evidence level 3).*

4.3. Radioisotope treatment

4.3.1. Duodenal neuroendocrine tumours

Isotope therapy with labelled somatostatin analogues is a form of palliative treatment rarely used in gastric NENs. The basic therapy in type 1 gastric NENs, whose form is usually polypoid, are endoscopic procedures, similarly to type 2 gastric NENs, which occur less frequently [49, 50].

Gastric neuroendocrine tumours type 1 are rarely associated with distant metastases, unlike type 2 gastric NENs, in which metastases can be present in 10–30% of patients already at the moment of diagnosis [49, 51]. Despite a low proliferation index, NENs G1 tend to recur, and the median recurrence-free survival is 24 months; however, the literature presents cases of transformation into NEC in 3% of patients [51]. The basic diagnostic tools in type 1 and 2 gastric NENs are endoscopy and EUS, used primarily to assess the depth of intramural invasion, mainly in tumours > 1–2 cm, before the endoscopic resection. Receptor scintigraphy examinations in these types of tumours do not show any significant clinical usefulness, except for less frequent large tumours, especially those invasive in EUS, or type 2 NENs in MEN1 syndrome [50–52].

Apart from surgical treatment, chemotherapy is the basic treatment of gastric neuronendocrine neoplasms type 3, in the case of disseminated disease [53]. Information on the possible use of targeted treatment with a labelled somatostatin analogue is very limited. The therapy may be introduced if high expression of somatostatin receptors on the neoplastic tumour cells is confirmed in a SPECT/PET examination, with somatostatin analogues in the case of disease progression/inoperative recurrence, and failure of other forms of treatment. Isotope diagnostics in this group of neoplasms enables determination of staging of the disease, and qualification to therapy with 'hot' somatostatin analogues; receptor scintigraphy performed after radionuclide therapy allows the assessment of its effectiveness [50, 54].

** evidence level according to CEBM [59]*

Among duodenal neuroendocrine tumours, the most frequently occurring ones are G1 tumours. G2 are less common, and NEC are rare (< 3% of cases). Duodenal NENs G1 are rarely metastatic; in the case of G2 tumours, the risk of hepatic and lymph nodes metastases increases, and in NEC metastases are present in 50–100% of cases. The basic form of therapy of duodenal NEN G1 and G2 is surgical treatment. To assess the staging of the disease, an imaging examination is performed during the follow-up, usually every 9–12 months, including the receptor test with a labelled somatostatin analogue. In metastatic duodenal G2 tumours, if surgical treatment of the primary tumour or metastases is impossible and the recurrence is inoperable, treatment with hot somatostatin analogues may be implemented. Eligibility for treatment is based on the confirmation of somatostatin receptors expression in isotope tests, and the lack of contraindications for such therapy. Detailed information on patient eligibility and PRRT can be found in the general section. It is also possible to apply this form of therapy in a case of a metastatic G1 tumour [9, 10, 18, 50, 51, 55–57].

In symptomatic tumours, treatment with 'cold' somatostatin analogues should also be considered. In metastatic duodenal NEC, if chemotherapy fails and/or the disease progresses, and/or such treatment is not tolerated, targeted radioisotope therapy may be implemented, provided the receptor expression is high [18, 51, 53].

5. Summary

Isotope therapy is rarely used in gastric tumours. Information on this subject is very limited. It may be taken into consideration in the case of gastric NEC with progression of the disease/inoperative recurrence and failure of chemotherapy and/or intolerance of this type of treatment, if high expression of somatostatin receptors is confirmed (**evidence level 4*).

In duodenal G2/G1 tumours, isotope therapy may be considered as the first-line therapy in the case of progression of the disease, if surgical treatment is impossible (**evidence level 3*).

In duodenal NEC, similarly to gastric G3 tumours, radionuclide therapy may be implemented if chemotherapy fails and/or the disease progresses, and/or such treatment is not tolerated, provided the receptor expression is high (**evidence level 4*).

Minimal consensus statement on isotope treatment:
The basic form of therapy in duodenal tumours is surgical treatment.
In the case of well-differentiated neoplasms of 1–2 cm, not infiltrating the muscularis propria in EUS examination, endoscopic excision is possible (endoscopic resection or submucosal dissection).
Isotope therapy as the first-line treatment, with disease progression, particularly in duodenal G1 and G2 tumours.
*In NEC, the treatment is considered individually, with progression of the disease and failure of other therapeutic methods, as well as with confirmed high expression of somatostatin receptors (*evidence level 4).*

Monitoring of the treatment
Minimal consensus statement on follow-up [58]:
Biochemical tests
Stomach:
— *type 1 and type 2: 1–3 year — anamnesis and physical examination every 6–12 months; 4–10 year anamnesis and physical examination every 12 months (*evidence level 3); type 3 and type 4:*
— *1 year: anamnesis and physical examination every 3–12 months (*evidence level 3); CgA every — 3–12 months (*evidence level 5);*
— *2–10 year: anamnesis and physical examination every 12 months (*evidence level 3), CgA every 12 months (*evidence level 5).*
Duodenum:
— *first year: every 3–12 months anamnesis and physical examination, CgA (*evidence level 5);*
— *2–10 year: every 6–12 months anamnesis and physical examination (*evidence level 3), CgA (*evidence level 5).*
Gastrinoma:
— *first year: every 3–12 months anamnesis and physical examination (*evidence level 3), gastrin (*evidence level 3), CgA (*evidence level 5);*
— *2-10 year: every 6–12 months anamnesis and physical examination (*evidence level 3), gastrin (evidence level 3), CgA (*evidence level 5).*
Diagnostic imaging
Stomach:
— *NEN type 1 and type 2: upper gastrointestinal endoscopy every 6–12 months, other imaging examinations (CT, MR) depending on the stage of the disease;*
— *NEN type 3 and type 4: upper gastrointestinal endoscopy every 3–6 months, other imaging examinations (CT, MR) every 3–6 months.*
Duodenum:
— *NEN G1, G2 — upper gastrointestinal endoscopy every 6–12 months, other imaging examinations (CT, MR), depending on the stage of the disease, every 6–12 months;*
— *NEC — upper gastrointestinal endoscopy every 3–6 months, other imaging examinations (CT, MR) every 3–6 months.*

** evidence level according to CEBM [59]*

References

1. Niederle MB, Hackl M, Kaserer K et al. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 2010; 17: 909– 918.
2. O'Toole D, Delle Fave GD, Jensen RT. Gastric and duodenal neuroendocrine tumours. Best Pract Res Clin Gastroenterol 2012; 26: 719–35.
3. Klöppel G. Tumour biology and histopathology of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metabol 2007; 21: 15–31.
4. Vannella L, Sbrozzi-Vanni A, Lahner E et al. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. Aliment Pharmacol Ther 2011; 33: 1361–1369.
5. Borch K, Ahren B, Ahlman H et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg 2005; 242: 64–73.
6. Merola E, Sbrozzi-Vanni A, Panzuto F et al. Type I gastric carcinoids: a prospective study on endoscopic management and recurrence rate. Neuroendocrinology 2012; 95: 207–213.
7. Rindi G, Arnold R, Bosman FT et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT et al. (eds.). WHO Classification of Tumours of the Digestive System. Lyon, IARC Press, 2010: 13–14.
8. Plöckinger U. Diagnosis and Treatment of Gastrinomas in Multiple Endocrine Neoplasia Type 1 (MEN-1). Cancers 2012; 4: 39–54.
9. Jensen RT, Rindi G, Arbold R et al. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). Neuroendocrinology 2006; 84: 165–172.
10. Ruszniewski P, Delle Fave G, Cadiot G et al. Well-differentiated gastric tumors/carcinomas. Neuroendocrinology 2006; 84: 158–164.
11. Ellison EC, Johnson JA. The Zollinger-Ellison syndrome: a comprehensive review of historical, scientific, and clinical considerations. Curr Probl Surg 2009; 46: 13–106.
12. Jensen RT, Niederle B, Mitry E et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology 2006; 84: 173–182.
13. Anlauf M, Garbrecht N, Henopp T et al. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinicopathological and epidemiological features. World J Gastroenterol 2006; 12: 5440–5446.
14. Thakker RV, Newey PJ, Walls GV et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97: 2990–3011.
15. Ramage JK, Ahmed A, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61: 6–32.
16. Jensen RT, Cadiot G, Brandi ML et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95: 98–119.
17. Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: Classification, functional syndromes, diagnosis and medical treatment. Best Pract Res Clin Gastroenterol 2005; 19: 675–697.
18. Kos-Kudla B, Bolanowski M, Handkiewicz-Junak D et al. Diagnostic and therapeutic guidelines for gastrointestinal neuroendocrine tumors (recommended by the Polish Network of Neuroendocrine Tumors). Endocrynol Pol 2008; 59: 41–56.
19. de Herder WW. Biochemistry of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21: 33–41.
20. Grozinsky-Glasberg S, Kaltsas G, Gur C et al. Long-acting somatostatin analogues are an effective treatment for type 1 gastric carcinoid tumours. Eur J Endocrinol 2008; 159: 475–482.
21. Washington K, Berlin J, Branton P et al. Protocol for the examination of specimens from patients with carcinoma of the stomach. In: Reporting on Cancer Specimens: Case Summaries and Background Documentation. Northfield, IL: College of American Pathologists; 2009.
22. Washington MK, Tang LH, Berlin J et al. Protocol for the Examination of Specimens From Patients With Neuroendocrine Tumors (Carcinoid Tumors) of the Stomach. Arch Pathol Lab Med 2010; 134: 187–191.
23. Gladdy RA, Strong VE, Coit D et al. Defining surgical indications for type I gastric carcinoid tumor. Ann Surg Oncol 2009; 16: 3154–60.
24. Rindi G, Kloppel G, Alhman H et al. TNM staging of foregut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449: 395–401.
25. Nasierowska-Guttmejer A. Nowa klasyfikacja NET. Onco Review 2011: 1: 46–50.
26. Oberg K, Akerstrom G, Rindi G et al. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl. 5): 223–227.
27. Nasierowska-Guttmejer A, Malinowska M. Guzy neuroendokrynne układu pokarmowego (GEP/NET) — dyskusja wokoł nazewnictwa i klasyfikacji. Przegl Gastroenterol 2006; 1: 1–4.
28. Nasierowska-Guttmejer A. Patomorfologia guzow neuroendokrynnych układu pokarmowego. Onkologia po Dyplomie 2005: 25–30.
29. Solcia E, Kloppel G, Sobin LH. In collaboration with 9 pathologists from 4 countries. Histological typing of endocrine tumours, 2nd edn. WHO international histological classification of tumours. Springer, Berlin 2000.
30. DeLellis RA, Lloyd RV, Hertz PU et al. Word Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs. IARC Press: Lyon 2004.
31. Rindi G, de Herder WW, O'Toole D et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumours: why such guidelines and how we went about it. Neuroendocrinology 2006; 84: 155–157.
32. Rindi G, Klopell G, Couvelard A et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a trading system. Virchows Arch 2007; 451: 757–762.
33. Delle Fave G, Kwekkeboom DJ, Van Cutsem E et al. ENETS Consensus Guidelines for the Management of Patients with Gastroduodenal Neoplasms. Neuroendocrinology 2012; 95: 74–87.
34. Annibale B, Azzoni C, Corleto VD et al. Atrophic body gastritis patients with enterochromaffin-like cell dysplasia are at increased risk for the development of type I gastric carcinoid. Eur J Gastroenterol Hepatol 2001; 13: 1449–1456.
35. Zimmer T, Ziegler K, Liehr RM et al. Endosonography of neuroendocrine tumors of the stomach, duodenum, and pancreas. Ann N Y Acad Sci 1994; 733: 425–436.
36. Pilch-Kowalczyk J, Leszczyński S. Układ trawienny. In: Diagnostyka obrazowa. Układ trawienny (ed.). Leszczyński S, Pilch-Kowalczyk J. PZWL, Warszawa 2012.
37. Ricke J, Klose KJ. Imaging procedures in neuroendocrine tumours. Digestion 2000; 62 (Suppl. 1): 39–44.
38. Reinig JW, Dwyer AJ, Miller DL et al. Liver metastasis detection: comparative sensitivities of MR imaging and CT scanning. Radiology 1987; 162: 43–47.
39. Wilcox CM, Seay T, Arcury JT et al. Zollinger-Ellison syndrome: presentation, response to therapy, and outcome. Dig Liver Dis 2011; 43: 439–443.
40. Yoshikane H, Suzuki T, Yoshioka N et al. Duodenal carcinoid tumor: endosonographic imaging and endoscopic resection. Am J Gastroenterol 1995; 90: 642–644.
41. Zimmer T, Stölzel U, Bader M et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. Gut 1996; 39: 562–568.
42. Khan RN, Bansal VK, Kumar S et al. Duodenal gastrinoma: a diagnostic dilemma. Am J Surg. 2009; 197: e48–50.
43. Acs G, McGrath CM, Gupta PK. Duodenal carcinoid tumor: report of a case diagnosed by endoscopic ultrasound-guided fine-needle aspiration biopsy with immunocytochemical correlation. Diagn Cytopathol 2000; 23: 183–186.
44. Lebtahi R, Cadiot G, Delahaye N et al. Detection of bone metastases in patients with endocrine gastroenteropancreatic tumors: bone scintigraphy compared with somatostatin receptor scintigraphy. J Nucl Med 1999; 40: 1602–1608.
45. Bordi C, Yu JY, Baggi MT et al. Gastric carcinoids and their precursor lesions. A histologic and immunohistochemical study of 23 cases. Cancer 1991; 67: 663–672.
46. Hartel W, Wente MN, Sido B et al. Carcinoid of the ampulla of Vater. J Gastroenterol Hepatol 2005; 20: 676–681.
47. Soga J. Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. J Exp Clin Cancer Res 2003; 22: 349–363.
48. Öberg K, Knigge U, Kwekkeboom D et al. Neuroendocrine gastroenteropancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2012; 23 (Suppl.7): vii124–vii 130.
49. La Rosa S, Inzani F, Vanoli A et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol 2011; 42: 1373–1384.
50. Rydzewska G, Cichocki A, Ćwikła J et al. Guzy endokrynne żołądka i dwunastnicy z uwzględnieniem gastrinoma. Endokrynol Pol 2008; 59: 57–67.
51. Fave G, Kwekkeboom D, Van Cutsem E et al. ENETS Consensus Guidelines for the Management of Patients with Gastroduodenal Neoplasms. Neuroendocrinology 2012; 95: 74–87.
52. Scherübl H, Jensen R, Cadiot G et al. Management of early gastrointestinal neuroendocrine neoplasms. World J Gastrointest Endosc 2011; 3: 133–139.
53. Pavel M, Baudin E, Couvelard A et al. ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms of Foregut, Midgut, Hindgut, and Unknown Primary. Neuroendocrinology 2012; 95: 157–176.
54. Krenning E, Kwekkeboom E, Valkema R et al. Peptide receptor radionuclide therapy. Ann. N.Y. Acad. Sci 2004; 1014: 234–245.
55. Baum RP, Söldner J, Schmücking M et al. Intravenous and Intra-arterial Peptide Receptor Radionuclide Therapy (PRRT) Using Y-90-DOTA-TYR3-OCTREOTATE (Y-90 DOTA-TATE) in Patients with Metastatic Neuroendocrine Tumors. Europ J Nucl Med Mol Imag 2004; 31: S238.

56. Kwekkeboom D, Teunissen J, Bakker W et al. Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate in Patients With Endocrine Gastroenteropancreatic Tumors. J Clin Oncol 2005; 23: 2754–2762.
57. Kwekkeboom D, Kam B, van Essen M et al. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocrine-Related Cancer 2010; 17: R53–R73.
58. O'Toole D, Grossman A, Gross D et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biochemical markers. Neuroendocrinology 2009; 90: 194–202.
59. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
60. Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653. *OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson.

List of Participants of the Consensus Conference on the 2013 Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms:

Elżbieta Andrysiak-Mamos (Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland), **Tomasz Bednarczuk** (Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland), **Jolanta Blicharz-Dorniak** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Marek Bolanowski** (Department of Endocrinology, Diabetology and Isotope Therapy, Medical University of Wroclaw, Wroclaw, Poland), **Jarosław B. Ćwikła** (Department of Radiology, Faculty of Medical Science, University of Varmia and Masuria, Olsztyn, Poland), **Andrzej Deptała** (Department of Oncology and Hematology, Central Clinical Hospital of the Ministry of Interior in Warsaw, Warsaw, Poland), **Daria Handkiewicz-Junak** (Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland), **Marek Hartleb** (Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland), **Michał Jarząb** (Department of Radiotherapy and Chemotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland), **Arkadiusz Jeziorski** (Department of Surgical Oncology, Medical University of Lodz, Poland), **Dariusz Kajdaniuk** (Division of Pathophysiology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Aldona Kowalska** (Department of Endocrinology, Holycross Cancer Centre, Kielce, Poland), **Robert Król** (Department of General, Vascular and Transplant Surgery, Medical University of Silesia, Katowice, Poland), **Leszek Królicki** (Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland), **Jolanta Kunikowska** (Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland), **Katarzyna Kuśnierz** (Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland), **Paweł Lampe** (Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland), **Dariusz Lange** (Department of Tumour Pathology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland), **Magdalena Londzin-Olesik** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Przemysław Majewski** (Department of Clinical Pathomorphology, Poznan University of Medical Sciences, Poznan, Poland), **Bogdan Marek** (Division of Pathophysiology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Gabriela Mełeń-Mucha** (Department of Immunoendocrinology, Chair of Endocrinology, Medical University of Lodz, Lodz, Poland), **Andrzej Nowak** (Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland), **Waldemar Patkowski** (Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland), **Violetta Rosiek** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Marek Ruchała** (Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland), **Sławomir Rudzki** (Department of General and Transplant Surgery and Nutritional Treatment, Medical University of Lublin, Lublin, Poland), **Philippe Ruszniewski** (Department of Gastroenterology, Hospital Beaujon, AP-HP, University Paris VII, Clichy, France), **Teresa Starzyńska** (Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland), **Katarzyna Steinhof-Radwańska** (Department of Radiology, Medical University of Silesia, Katowice, Poland), **Janusz Strzelczyk** (Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Wojciech Zajęcki** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Piotr Zdunowski** (Department of Endocrinology, The Centre of Postgraduate Medical Education, Warsaw, Poland), **Anna Zemczak** (Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice).